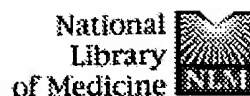


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DT Utility; Patent Application - First Publication  
FS CHEMICAL  
APPLICATION  
CLMN 14  
AB The present invention provides compounds of formula (I)

#### D R A W I N G

the prodrugs thereof, and the pharmaceutically acceptable salts of the  
compounds and prodrugs, wherein Ra, Rb, R1, and R2 are as defined herein;  
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PA Ono Pharmaceutical Co., Ltd., Japan

SO PCT Int. Appl., 22 pp.

CODEN: PIXXD2

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	W:				
	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,				
	CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,				
	GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS,				
	LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL,				
	PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA,				
	UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,  
CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,  
PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,  
NE, SN, TD, TG

EP 1415668 A1 20040506 EP 2002-746090 20020716  
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,  
IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK  
US 2004176347 A1 20040909 US 2004-483629 20040114  
PRAI JP 2001-217755 A 20010718  
WO 2002-JP7212 W 20020716

OS MARPAT 138:131143

AB Remedies and/or preventives for brain ischemic diseases comprising two active ingredients, namely, an astrocytic function-improving agent, preferably a compound represented by Et(CH<sub>2</sub>)<sub>n</sub>C(R<sub>5</sub>R<sub>11</sub>)COR<sub>6</sub> (I), and a thrombolytic agent, preferably a tissue plasminogen activator: I wherein R<sub>6</sub> = OH, etc.; and (1) n = 1, R<sub>11</sub> = H, and R<sub>5</sub> = alkyl (having a fluorine atom as a substituent of a carbon atom)-CH<sub>2</sub>-; or (2) n = 0 or 1, R<sub>11</sub> = H, etc., and R<sub>5</sub> = alkyl, etc. These drugs show synergistic therapeutic effects compared with the case where an astrocytic function improving agent and a thrombolytic agent are sep. administered.

RE.CNT 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 3 OF 37 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 3

AN 2003:827900 CAPLUS

DN 140:122653

TI Ebselen, a seleno-organic antioxidant, is neuroprotective after embolic strokes in rabbits: Synergism with low-dose tissue plasminogen activator

AU Lapchak, Paul A.; Zivin, Justin A.

CS Department of Neuroscience, University of California San Diego, La Jolla, CA, USA

SO Stroke (2003), 34(8), 2013-2018

CODEN: SJCCA7; ISSN: 0039-2499

PB Lippincott Williams & Wilkins

DT Journal

LA English

AB It has been proposed that antioxidants and spin-trap agents may be neuroprotective after acute ischemic stroke. Although the antioxidant ebselen is currently in clin. trials, little is known about the effectiveness of ebselen, which has glutathione peroxidase-like and antiinflammatory properties in embolic stroke models. Therefore, we determined the effects of ebselen when administered alone or with the thrombolytic tissue plasminogen activator (tPA), the only Food and Drug Administration-approved pharmacol. agent for the treatment of stroke. Male New Zealand White rabbits were embolized by injection of a suspension of small blood clots into the middle cerebral artery via a catheter. Five minutes after embolization, ebselen (10 to 50 mg/kg) was infused i.v. Control rabbits received infusions of the vehicle required to solubilize ebselen. In addnl. rabbits, ebselen (20 mg/kg) was administered 60 min after embolization, either alone or in combination with tPA (0.9 or 3.3 mg/kg tPA). Behavioral anal. was conducted 24 h after embolization, allowing determination of the effective stroke dose (P50) or clot amount (mg)

that produces neurol. deficits in 50% of the rabbits. A drug is considered neuroprotective if it significantly increases the P50 compared with the vehicle-treated control group. The P50 of controls 24 h after embolization was 1.35±0.30 mg. Rabbits treated 5 min after embolization with 10, 20, or 50 mg/kg ebselen had P50 values of 2.12±0.56, 2.82±0.75 (P<0.05), and 0.49±0.54 mg, resp. A significant neuroprotective effect was observed with the 20-mg/kg dose, but not if there was a 60-min delay before administration (P50=1.69±0.32 mg). When tPA (3.3 mg/kg) was infused 60 min after embolization and ebselen (20 mg/kg) was injected at either 5 (P50=2.98±0.18 mg) or 60

( $P_{50}=3.60\pm0.79$  mg) minutes, there was no addnl. neuroprotective effect compared with tPA alone ( $P_{50}=3.38\pm0.55$  mg). However, if ebselen (20 mg/kg) was administered concomitantly with low-dose tPA (0.9 mg/kg) 60 min after embolization, the  $P_{50}$  was  $3.52\pm0.73$  mg ( $P<0.05$ ), indicating a synergistic effect of the drug combination because neither alone was effective ( $P_{50}=1.69\pm0.32$  and  $1.54\pm0.36$  mg, resp.). This study indicates that ebselen may be neuroprotective when administered shortly after an embolic stroke, but the time- and dose-response analyses suggest that it has a narrow therapeutic window. Nevertheless, ebselen may be beneficial if administered concomitantly with a thrombolytic because it significantly enhanced the neuroprotective activity of low-dose tPA.

RE.CNT 31      THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3      ANSWER 4 OF 37    CAPLUS    COPYRIGHT 2004 ACS on STN DUPLICATE 4

AN      2003:498080    CAPLUS

DN      140:70312

TI      Effects of a Selective CD11b/CD18 Antagonist and Recombinant Human Tissue Plasminogen Activator Treatment Alone and in Combination in a Rat Embolic Model of Stroke

AU      Zhang, Li; Zhang, Zheng Gang; Zhang, Rui Lan; Lu, Mei; Krams, Michael; Chopp, Michael

CS      Departments of Neurology, Henry Ford Health Sciences Center, Detroit, MI, USA

SO      Stroke (2003), 34(7), 1790-1795

CODEN: SJCCA7; ISSN: 0039-2499

PB      Lippincott Williams & Wilkins

DT      Journal

LA      English

AB      The authors evaluated the neuroprotective effect of UK-279,276 (also referred to as recombinant neutrophil inhibitory factor), a selective CD11b/CD18 antagonist, in combination with thrombolytic therapy on focal cerebral ischemia. Male Wistar rats ( $n=88$ ) were subjected to embolic middle cerebral artery occlusion. Animals were randomly assigned to the following groups ( $n=11$  in each group): vehicle treatment alone at 2 or 4 h, UK-279,276 treatment alone at 2 or 4 h, recombinant human tissue plasminogen activator (rhtPA) treatment alone at 2 or 4 h, or the combination of UK-279,276 and rhtPA at 2 or 4 h. Infarct volume, neurol. function, hemorrhagic transformation, neutrophil accumulation, and parenchymal fibrin deposition were measured 7 days after middle cerebral artery occlusion. Treatment with UK-279,276 significantly ( $P<0.05$ ) improved neurol. severity scores, an index of neurol. functional deficit, but had no effect on infarct volume compared with vehicle-treated animals. Treatment with rhtPA alone at 2 but not 4 h significantly ( $P<0.05$ ) reduced infarct volume and improved neurol. function compared with vehicle-treated animals. Combination treatment with UK-279,276 and rhtPA at 2 or 4 h significantly ( $P<0.01$ ) reduced infarct volume and enhanced recovery of neurol. function compared with control. Neutrophil accumulation and fibrin deposition in the brain parenchyma of combination-treated rats at 2 and 4 h after stroke were significantly reduced ( $P<0.05$ ) compared with corresponding vehicle-treated control groups. The neuroprotective effect of the combined treatments was superior to the additive effects from each treatment of rhtPA or UK-279,276 alone. These data suggest that the combination treatment with UK-279,276 and rhtPA may extend the window of thrombolytic therapy for the acute treatment of stroke.

RE.CNT 32      THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3      ANSWER 5 OF 37    CAPLUS    COPYRIGHT 2004 ACS on STN DUPLICATE 5

AN      2003:526970    CAPLUS

DN      139:345804

TI      Recombinant human tissue plasminogen activator protects the basal lamina in experimental focal cerebral ischemia

AU Burggraf, Dorothe; Martens, Helge K.; Jaeger, Gabriele; Hamann, Gerhard F.  
CS Department of Neurology, Ludwig-Maximilians-University Munich, Klinikum  
Grosshadern, Munich, Germany  
SO Thrombosis and Haemostasis (2003), 89(6), 1072-1080  
CODEN: THHADQ; ISSN: 0340-6245  
PB Schattauer GmbH  
DT Journal  
LA English  
AB While recombinant tissue plasminogen activator (rt-PA) is successfully  
used in human ischemic stroke, it may also cause hemorrhagic  
complications. Animal expts. have shown that hemorrhages are related to  
microvascular basal lamina damage. We investigated the effects of  
different doses of rt-PA on the brain microvasculature. Exptl. cerebral  
ischemia in rats was induced for 3 h and followed by 24 h reperfusion  
(suture model). Each group of rats (n = 6) received either treatment  
(0.9, 9, or 18 mg rt-PA/kg body weight) or saline (control group) at the end  
of ischemia. The loss of microvascular basal lamina antigen collagen type  
IV was measured by Western blot of the ischemic and non-ischemic basal  
ganglia and cortex. Compared with the contralateral non-ischemic area,  
collagen type IV was significantly reduced in the ischemic area: (basal  
ganglia/cortex) 43% +/- 9% / 64% +/- 4%. Low/moderate doses of rt-PA had  
a protective effect: 0.9 mg 79% +/- 3% / 89% +/- 6%, 9 mg 72% +/- 9% / 81%  
+/- 12% (p < 0.05). Higher doses of rt-PA (18 mg) had a similar effect as  
seen in untreated controls: 57% +/- 11% / 59% +/- 9% (p < 0.05, Anova).  
MMP-9 and MMP-2, measured by gelatine zymog., steadily increased over  
higher doses of rt-PA; MMP-9 (basal ganglia/cortex): control I 15% +/- 4%  
/ 123% +/- 3% compared with 18 mg rt-PA 146% +/- 5% / 162% +/- 6% (p <  
0.05) and MMP-2: control 109% +/- 4% / 116% +/- 5% and 18 mg rt-PA 222% +/-  
15% / 252% +/- 2% (p < 0.05). Low to moderate doses of rt-PA protect the  
microvascular basal lamina, whereas high doses of rt-PA have the opposite  
effect, probably due to increased coactivation of MMP-2 and MMP-9.

RE.CNT 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 6 OF 37 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on  
STN  
AN 2004:198959 BIOSIS  
DN PREV200400199518  
TI S100b correlates with clinical outcomes in ischemic stroke.  
AU Krams, M. [Reprint Author]; Body, C. [Reprint Author]; Gao, F. [Reprint  
Author]; Soares, H. D. [Reprint Author]  
CS Clin. Sci. CNS, Pfizer, Groton, CT, USA  
SO Society for Neuroscience Abstract Viewer and Itinerary Planner, (2003)  
Vol. 2003, pp. Abstract No. 412.16. <http://sfn.scholarone.com>. e-file.  
Meeting Info.: 33rd Annual Meeting of the Society of Neuroscience. New  
Orleans, LA, USA. November 08-12, 2003. Society of Neuroscience.  
DT Conference; (Meeting)  
Conference; Abstract; (Meeting Abstract)  
LA English  
ED Entered STN: 14 Apr 2004  
Last Updated on STN: 14 Apr 2004  
AB Stroke is the second leading cause of death in the United States and it is  
estimated that over 750,000 subjects per year suffer from a stroke in the  
US alone. Inter-rater variability and misclassification errors may  
contribute, in part, to the failure to establish a safe and efficacious  
neuroprotectant treatment. Considerable effort has gone into validating  
biomarkers that correlate with therapeutic efficacy, infarct volume and  
clinical outcome measures. This report presents a post-hoc analysis of  
plasma S100B as a possible prognostic variable of clinical outcome in  
acute ischemic stroke patients enrolled within 6 hours into a double-blind  
placebo controlled dose-response finding study of a neuroprotectant. 21%  
of all patients received concomitant tPA treatment. Whilst the  
neuroprotectant did not yield a significant treatment benefit, tPA was

found to be a significant covariate with an additional improvement of 1.6 points on the Scandinavian Stroke Scale (SSS) from baseline to day 90 in tPA treated patients. Patients receiving either tPA alone or tPA and the neuroprotectant (n = 195) were contrasted with patients who did not receive tPA nor the neuroprotectant (n = 159) to determine whether S100B could provide an early indication of therapeutic efficacy. Plasma samples were collected at baseline, 1, 3, 7 and 21 days from the start of study drug infusion. S100B values peaked at 3 days and returned to baseline levels by 21 days post injury. Three day S100B levels correlated with infarct volume as assessed by 5 day CT scans. In addition, S100B correlated with 90 day Bartel, Modified Rankin, SSS and National Institute of Health Stroke Scale clinical outcome measures. Interestingly, neither infarct volume nor S100B levels were significantly different between tPA and non-tPA treated groups. Nevertheless, inclusion of S100B levels in logistic regression models increased the sensitivity and specificity of predicting clinical outcome at 90 days post-injury suggesting that S100B has some utility in prediction models.

L3 ANSWER 7 OF 37 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 6  
 AN 2002:532764 CAPLUS  
 DN 138:100640  
 TI Effects of the spin trap agent disodium- [(tert-butylimino)methyl]benzene-1,3-disulfonate N-oxide (generic NXY-059) on intracerebral hemorrhage in a rabbit large clot embolic stroke model. Combination studies with tissue plasminogen activator  
 AU Lapchak, Paul A.; Araujo, Dalia M.; Song, Donghuan; Wei, Jiandong; Purdy, Robert; Zivin, Justin A.  
 CS Department of Neuroscience, University of California at San Diego, San Diego, CA, USA  
 SO Stroke (2002), 33(6), 1665-1670  
 CODEN: SJCCA7; ISSN: 0039-2499  
 PB Lippincott Williams & Wilkins  
 DT Journal  
 LA English  
 AB Background and Purpose-It was proposed that the novel spin trap agent disodium-[(tertbutylimino)methyl]benzene-1,3-disulfonate N-oxide (NXY-059) may be useful in the treatment of ischemia and stroke. To date, there is little information concerning the safety of NXY-059 when administered in combination with the only Food and Drug Administration-approved pharmacol. agent for the treatment of stroke, the thrombolytic tissue plasminogen activator (tPA). Thus, the authors determined the effects of NXY-059G, a generic form of NXY-059, on hemorrhage and infarct rate and volume when administered alone or in combination with tPA. In addition, the authors determined whether NXY-059G affected 2 physiol. variables, blood glucose levels and body temperature. Methods-Male New Zealand White rabbits were embolized by injecting a large blood clot into the middle cerebral artery via a catheter. Five minutes after embolization, NXY-059G (100 mg/kg) was infused i.v.; control rabbits received infusions of saline, the vehicle required to solubilize NXY-059G. In tPA studies, the thrombolytic was administered i.v. starting 60 min after embolization (20% bolus injection/80% infusion over 30 min). Body temperature and blood glucose levels were measured throughout the study. Postmortem anal. included assessment of hemorrhage and infarct rate, size, and location. Results-In the vehicle control group, the hemorrhage rate after a thromboembolic stroke was 52% (n=23), and this was increased by 67% if tPA was administered (n=15). The rabbits treated with NXY-059G in the absence of tPA had a 79% incidence of hemorrhage (n=19), an increase of 52% over the control group. In the combination drug-treated groups, the NXY-059G/tPA group had a 47% incidence of hemorrhage (n=15). There was a decrease of hemorrhage volume in the NXY-059G+tPA group compared with the other 3 groups included in the study. There was no significant effect of NXY-059G either alone or in combination with tPA on infarct rate or volume. NXY-059G did not significantly alter the physiol. variables that were measured.



Conclusions-This study suggests that NXY-059G may affect the integrity of the cerebral vasculature when administered immediately after an embolic stroke, as evidenced by an increase in hemorrhage rate. However, when NXY-059G is administered in combination with tPA, it may improve the safety of tPA by reducing the incidence of tPA-induced hemorrhage. The mechanism(s) involved in the NXY-059G-induced increase in hemorrhage rate and reduction of tPA-induced hemorrhage rate remains to be elucidated.

RE.CNT 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 8 OF 37 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 7

AN 2002:420526 CAPLUS

DN 138:33204

TI Neuroprotective effects of the spin trap agent disodium-[(tert-butylimino)methyl]benzene-1,3-disulfonate N-oxide (generic NXY-059) in a rabbit small clot embolic stroke model: combination studies with the thrombolytic tissue plasminogen activator

AU Lapchak, Paul A.; Araujo, Dalia M.; Song, Donghuan; Wei, Jiandong; Zivin, Justin A.

CS Department of Neuroscience, University of California at San Diego, San Diego, CA, USA

SO Stroke (2002), 33(5), 1411-1415

CODEN: SJCCA7; ISSN: 0039-2499

PB Lippincott Williams & Wilkins

DT Journal

LA English

AB Background and Purpose-It was proposed that the novel spin trap agent disodium-[(tert-butylimino)methyl]benzene-1,3-disulfonate N-oxide (NXY-059) may be useful in the treatment of ischemic stroke. However, there is little information concerning the neuroprotective properties of NXY-059 when administered after an embolic stroke. Moreover, there is no information available concerning the combination of NXY-059 with the only Food and Drug Administration-approved pharmacol. agent for the treatment of acute stroke, the thrombolytic tissue plasminogen activator (tPA). Thus, the authors determined the effects of NXY-059G, a generic form of NXY-059, on behavioral outcome after an embolic stroke when administered alone or in combination with tPA. Methods-Male New Zealand White rabbits were embolized by injecting a suspension of small blood clots into cerebral circulation via a carotid catheter. NXY-059G (100 mg/kg) was infused i.v. 5 min or 3 h after embolization, whereas control rabbits received infusions of the saline vehicle. In tPA studies, the thrombolytic was administered i.v. starting 60 min or 3 h after embolization (3.3 mg/kg). In combination studies, NXY-059G was given 5 min after embolization, followed by the administration of tPA beginning either 60 min or 3 h after embolization. Behavioral anal. was conducted 24 h after embolization. Results-In the vehicle control group, the ES50 value (calculated as the amount of microclots [milligrams] that produce neurol. dysfunction [impairment] in 50% of the rabbits within a specific treatment group) measured 24 h after embolism was 1.04 mg, and this was increased by 153% to 2.54 mg if NXY-059G was administered beginning 5 min after embolization. However, if NXY-059G was administered beginning 3 h after embolization, the ES50 was 2.01 mg. The rabbits treated with tPA alone had an ES50 of 2.64 or 0.63 mg if tPA administration started 60 min or 3 h after embolization, resp. If tPA was administered after NXY-059G (started at 5 min), the ES50 values were 3.15 or 2.66 if tPA administration started 60 min or 3 h after embolization, resp. Conclusions-This study suggests that NXY-059G is neuroprotective and can increase behavioral ratings if administered early after an embolic stroke. In addition, the study shows that NXY-059G can be used in combination with tPA without neg. side effects. The drug combination can improve behavioral function and increase ES50 values. However, during the short time course of the behavioral anal., the combination was not statistically better than either drug alone.

RE.CNT 23      THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3      ANSWER 9 OF 37    CAPLUS    COPYRIGHT 2004 ACS on STN DUPLICATE 8

AN      2002:110307    CAPLUS

DN      137:163707

TI      The nonpeptide glycoprotein IIb/IIIa platelet receptor antagonist SM-20302 reduces tissue plasminogen activator-induced intracerebral hemorrhage after thromboembolic stroke

AU      Lapchak, Paul A.; Araujo, Dalia M.; Song, Donghuan; Zivin, Justin A.

CS      Department of Neuroscience, University of California at San Diego, La Jolla, CA, 92093-0624, USA

SO      Stroke (2002), 33(1), 147-152

      CODEN: SJCCA7; ISSN: 0039-2499

PB      Lippincott Williams & Wilkins

DT      Journal

LA      English

AB      Platelet activation and deposition in brain microvessels appear to be key events in the pathogenesis of ischemia-induced neuronal degeneration and behavioral deficits. It has been hypothesized that activated platelets in combination with polymorphonuclear leukocytes and fibrin may play a role in vessel reocclusion leading to the "no-reflow" phenomenon after administration of the thrombolytic tissue plasminogen activator (tPA). We studied the effects of the novel glycoprotein IIb/IIIa platelet receptor antagonist SM-20302 when administered in combination with tPA on infarct and hemorrhage rate and volume to determine whether activated platelets are involved in either infarct or hemorrhage generation after a thromboembolic stroke. One hundred thirty-two male New Zealand White rabbits were included in the present study. Rabbits were embolized by injecting a blood clot into the middle cerebral artery via a catheter. Five or 65 min after embolization, SM-20302 (5 mg/kg) was infused i.v. In drug combination studies, tPA was infused i.v. for 30 min starting 60 min after embolization, and SM-20302 was administered 5 or 65 min after embolization. Postmortem anal. included assessment of hemorrhage, infarct size and location, and clot lysis. In the vehicle control group, the hemorrhage rate after a thromboembolic stroke was 33%. There was a significant increase (109%) in the hemorrhage rate in the group of rabbits treated with the thrombolytic tPA. SM-20302 by itself did not significantly alter the embolism-induced hemorrhage rate when administered either 5 or 65 min after embolism. The SM-20302 groups had a 42% and 33% incidence of hemorrhage in the 5- and 65-min groups, resp. In groups treated with a combination of drugs, the SM-20302/tPA group had a 31% and 71% incidence of hemorrhage when SM-20302 was administered 5 and 65 min after embolization, resp. SM-20302 in combination with tPA also significantly increased infarct rate, but not hemorrhage or infarct volume. This study suggests that treatment of thromboembolic stroke with the combination of a platelet inhibitor and tPA may have a beneficial outcome on the basis of the following: First, acute administration of SM-20302 did not significantly increase hemorrhage rate. Second, SM-20302 in combination with tPA significantly reduced tPA-induced intracerebral hemorrhage. Third, there appears to be a specific window of opportunity when a platelet inhibitor must be administered to produce a beneficial effect. Overall, on the basis of our results, we hypothesize that the increased rate of intracerebral hemorrhage observed after tPA administration may be partly due to increased reocclusion of cerebral vessels following lysis of the emboli and that reocclusion can be controlled by administration of a platelet inhibitor.

RE.CNT 36      THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3      ANSWER 10 OF 37    BIOSIS    COPYRIGHT (c) 2004 The Thomson Corporation. on STN

AN      2002:196409    BIOSIS

DN PREV200200196409  
 TI Serum tau protein level as a marker of axonal damage in acute ischemic stroke.  
 AU Bitsch, Andreas [Reprint author]; Horn, Claudia; Kemmling, Yvonne; Seipelt, Maria; Hellenbrand, Uwe; Stiefel, Michael; Ciesielczyk, Barbara; Cepek, Lukas; Bahn, Erik; Ratzka, Peter; Prange, Hilmar; Otto, Markus  
 CS Neurologische Klinik, Ruppiner Kliniken GmbH, Fehrbelliner Strasse 38, D-16816, Neuruppin, Germany  
 abitsch@t-online.de  
 SO European Neurology, (January, 2002) Vol. 47, No. 1, pp. 45-51. print.  
 CODEN: EUNEAP. ISSN: 0014-3022.  
 DT Article  
 LA English  
 ED Entered STN: 13 Mar 2002  
 Last Updated on STN: 13 Mar 2002  
 AB Biochemical markers of brain damage, e.g. ischemic stroke, should reflect the volume of irreversibly damaged brain parenchyma and the clinical outcome in a single patient in order to allow estimation of prognosis at an early stage. Tau protein, which derives predominantly from neurons and axons, is elevated in the cerebrospinal fluid of patients with neurodegenerative disease. This makes tau protein a potential marker of neuronal/axonal injury. In order to test this hypothesis, the current study aimed at showing that tau protein is measurable in the blood after acute ischemic stroke and that it correlates with clinical disability and stroke volume. In a longitudinal prospective study we measured tau protein serum levels with an ELISA in 30 patients longitudinally after ischemic stroke. Tau protein was detectable within 5 days after ischemia in the sera of 7/20 patients with MRI-proven infarction and in 2/10 patients with transitory ischemic attack; both of them had a small infarction visible on the MRI scan. Tau protein was measurable within 6 h after symptom onset, peaked after 3-5 days and correlated with infarct volume and disability after 3 months. In conclusion, serum tau protein is a candidate marker of axonal injury. In stroke, its clinical use is limited, because it is detectable only in a proportion of patients.

L3 ANSWER 11 OF 37 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on  
 STN DUPLICATE 9  
 AN 2002:95392 BIOSIS  
 DN PREV200200095392  
 TI Postischemic (6-hour) treatment with recombinant human tissue plasminogen activator and proteasome inhibitor PS-519 reduces infarction in a rat model of embolic focal cerebral ischemia.  
 AU Zhang, Li; Zhang, Zheng Gang; Zhang, Rui Lan; Lu, Mei; Adams, Julian; Elliott, Peter J.; Chopp, Michael [Reprint author]  
 CS Neurology Department, Henry Ford Hospital, 2799 W Grand Blvd, Detroit, MI, 48202, USA  
 chopp@neuro.hfh.edu  
 SO Stroke, (December, 2001) Vol. 32, No. 12, pp. 2926-2931. print.  
 CODEN: SJCCA7. ISSN: 0039-2499.  
 DT Article  
 LA English  
 ED Entered STN: 24 Jan 2002  
 Last Updated on STN: 25 Feb 2002  
 AB Background and Purpose: The proteasome inhibitor PS-519 blocks activation of nuclear factor-kappaB, a major mediator of inflammation. We tested the hypothesis that combination treatment of recombinant human tissue plasminogen activator (rhtPA) and PS-519 extends the therapeutic window for treatment of stroke with rhtPA without increasing incidence of hemorrhagic transformation. Methods: The middle cerebral artery (MCA) of male Wistar rats (n=56) was occluded by an embolus. After embolization, animals were randomly divided into the following groups: PS-519 treatment groups: PS-519 was given at 2, 4, or 6 hours after MCA occlusion; rhtPA treatment groups: rhtPA was given at 2 or 4 hours after MCA occlusion;

combination treatment groups: PS-519 and rhtPA were given at 2, 4, or 6 hours after MCA occlusion; control group: the same volume of saline was given at 2 hours after MCA occlusion. Results: Administration of PS-519 alone at 2 or 4 hours, but not 6 hours, significantly ( $P<0.05$ ) reduced infarct volume and improved neurological recovery compared with the control group. Administration of rhtPA alone at 2 hours, but not 4 hours, significantly ( $P<0.05$ ) reduced infarct volume and improved neurological recovery compared with the control group. Furthermore, combination treatment with rhtPA and PS-519 even at 6 hours significantly ( $P<0.05$ ) reduced infarct volume, improved neurological recovery, and did not increase the incidence of hemorrhagic transformation compared with the control group or the group treated with PS-519 alone. Conclusions: Our data suggest that combination treatment with PS-519 and rhtPA extends the neuroprotective effect to at least 6 hours after embolization.

L3 ANSWER 12 OF 37 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on  
STN DUPLICATE 10  
AN 2001:547636 BIOSIS  
DN PREV200100547636  
TI Zinc and tissue plasminogen activator interactions in the mammalian CNS.  
AU Siddiq, M. M. [Reprint author]; Tsirka, S. E. [Reprint author]  
CS Program in MCB, University at Stony Brook, Stony Brook, NY, USA  
SO Society for Neuroscience Abstracts, (2001) Vol. 27, No. 1, pp. 1484.  
print.  
Meeting Info.: 31st Annual Meeting of the Society for Neuroscience. San  
Diego, California, USA. November 10-15, 2001.  
ISSN: 0190-5295.  
DT Conference; (Meeting)  
Conference; Abstract; (Meeting Abstract)  
LA English  
ED Entered STN: 21 Nov 2001  
Last Updated on STN: 25 Feb 2002  
AB Delivery of exogenous zinc into the mammalian brain leads to neuronal  
death. The mechanism of this cell death is not yet understood. Zinc  
toxicity is attenuated with the addition of tissue plasminogen activator  
(tPA), an extracellular serine protease. A tPA/plasmin proteolytic  
cascade has been shown to promote excitotoxin-induced neurodegeneration.  
However, the attenuation of zinc toxicity by tPA was observed even in the  
absence of tPA's proteolytic activity. To obtain a better understanding  
of the way these two modulators of neuronal death work, we investigated  
the possible interactions between zinc and tPA both in culture and in  
vivo. First we evaluated the effect of zinc on the tPA's proteolytic  
activity: tPA is inhibited in a dose-dependent fashion by zinc.  
Furthermore, tPA can be purified on zinc-agarose columns. These two  
pieces of evidence suggest a direct interaction between zinc and tPA, with  
tPA possibly functioning as a chelator for free zinc. Exposure to high  
concentrations of zinc resulted in toxicity in both wild-type and tPA-/-  
mixed cortical cultures. tPA-/- mice-derived cultures were more sensitive  
to zinc compared to wild-type ones. This higher sensitivity could  
possibly be due to the presence of elevated amounts of free zinc in the  
cultures that lack tPA. One could speculate in the case of  
non-proteolytic neuroprotection against zinc by tPA that the excess free  
zinc is being chelated by tPA, and correspondingly, in the case of active  
tPA, that zinc, either directly or indirectly (as a chaperone of a serine  
protease inhibitor), inactivates the tPA.

L3 ANSWER 13 OF 37 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 11  
AN 2001:803094 CAPLUS  
DN 136:112454  
TI The Clomethiazole Acute Stroke Study in tissue-type plasminogen  
activator-treated stroke (CLASS-T): final results  
AU Lyden, P.; Jacoby, M.; Schim, J.; Albers, G.; Mazzeo, P.; Ashwood, T.;  
Nordlund, A.; Odergren, T.

CS CLASS IHT Investigators, Department of Neurosciences, UCSD School of  
Medicine, Veterans Administration Medical Center, San Diego, CA, USA  
SO Neurology (2001), 57(7), 1199-1205  
CODEN: NEURAI; ISSN: 0028-3878  
PB Lippincott Williams & Wilkins  
DT Journal  
LA English  
AB Aim of this study was to assess the safety of tissue-type plasminogen  
activator (t-PA) plus clomethiazole in patients with acute ischemic stroke  
and determine the feasibility of combination stroke therapy. Clomethiazole is  
a neuroprotectant that appeared to improve outcome in patients with clin.  
deficits of a major stroke (total anterior circulation syndrome [TACS]) in  
a previous study, the Clomethiazole Acute Stroke Study (CLASS). Combining  
a neuroprotectant such as clomethiazole with thrombolysis may augment the  
beneficial effects of the two agents. CLASS-t-PA (CLASS-T) was a pilot  
study to explore the safety of the combination and the feasibility of  
performing combination treatment in the setting of acute ischemic stroke.  
In a randomized, double-blind design (stratified for age, severity at  
admission, and time since onset of stroke), all patients received 0.9  
mg/kg t-PA beginning within 3 h of stroke onset and then either 68 mg/kg  
clomethiazole (n = 97) i.v. over 24 h or placebo (n = 93) beginning within  
12 h of stroke onset. Patients were followed for 90 days. The main  
measures of safety were mortality and serious adverse events, and the main  
measure of functional outcome was the Barthel Index. The number of serious  
adverse event reports was 47 in the clomethiazole group and 48 in the  
placebo group. Death during the 90 days after treatment occurred in 15  
clomethiazole and nine placebo patients (p = 0.26). Sedation was reported  
as an adverse event during therapy in 42% of clomethiazole patients vs.  
13% of placebo patients. The proportion of patients with TACS was 53% in  
the clomethiazole group and 41% in the placebo group. In the TACS  
subgroup, 52.9% of the clomethiazole patients scored a Barthel Index  
greater than 60 vs. 44.7% of placebo patients (odds ratio 1.39; 95% CI  
0.60 to 3.23). In this pilot study, there were no safety concerns related  
to the combination of t-PA and clomethiazole. The combination paradigm  
proved feasible, although many patients received clomethiazole several  
hours after thrombolysis; future studies must require prompt  
administration of the neuroprotectant either before or during  
administration of the thrombolytic. Patients with major strokes (TACS)  
may have the potential to benefit from the combination of t-PA and  
clomethiazole.

RE.CNT 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 14 OF 37 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on  
STN  
AN 2001:361564 BIOSIS  
DN PREV200100361564  
TI Apolipoprotein E phenotype and the efficacy of intravenous tissue  
plasminogen activator in acute ischemic stroke.  
AU Broderick, Joseph [Reprint author]; Lu, Mei; Jackson, Christy; Pancioli,  
Arthur; Tilley, Barbara C.; Fagan, Susan C.; Kothari, Rashmi; Levine,  
Steven R.; Marler, John R.; Lyden, Patrick D.; Haley, E. Clark, Jr.;  
Brott, Thomas; Grotta, James C.  
CS Department of Neurology, University of Cincinnati, 231 Bethesda Ave., ML  
0525, Cincinnati, OH, 45267-0525, USA  
joseph.broderick@uc.edu  
SO Annals of Neurology, (June, 2001) Vol. 49, No. 6, pp. 736-744. print.  
CODEN: ANNED3. ISSN: 0364-5134.  
DT Article  
LA English  
ED Entered STN: 2 Aug 2001  
Last Updated on STN: 19 Feb 2002  
AB We used stored plasma samples from 409 patients in the National Institute

of Neurological Diseases and Stroke (NINDS) tissue plasminogen activator (t-PA) Stroke Trial to examine the relationship between an apolipoprotein (Apo) E2 or an Apo E4 phenotype and a favorable outcome 3 months after stroke, the risk of intracerebral hemorrhage, and the response to intravenous t-PA therapy. For the 27 patients with an Apo E2 phenotype who were treated with t-PA, the odds ratio (OR) of a favorable outcome at 3 months was 6.4 (95% confidence interval (CI) 2.7-15.3%) compared to the 161 patients without an Apo E2 phenotype who were treated with placebo. The 190 patients treated with t-PA who did not have an Apo E2 phenotype also had a greater, though less pronounced, likelihood of a favorable outcome (OR 2.0, 95% CI 1.2-3.2%) than patients without an Apo E2 phenotype treated with placebo. For the 31 patients with an Apo E2 phenotype treated with placebo, the OR of a favorable 3 month outcome was 0.8 (95% CI 0.4-1.7%) compared to the 161 patients without an Apo E2 phenotype treated with placebo. This interaction between treatment and Apo E2 status persisted after adjustment for baseline variables previously associated with 3 month outcome, for differences in the baseline variables in the two treatment groups and in the Apo E2-positive and -negative groups, and for a previously reported time-to-treatment X treatment interaction ( $p = 0.03$ ). Apo E4 phenotype, present in 111 (27%) of the 409 patients, was not related to a favorable 3 month outcome, response to t-PA, 3 month mortality, or risk of intracerebral hemorrhage. We conclude that the efficacy of intravenous t-PA in patients with acute ischemic stroke may be enhanced in patients who have an Apo E2 phenotype, whereas the Apo E2 phenotype alone is not associated with a detectable benefit on stroke outcome at 3 months in patients not given t-PA. In contrast to prior studies of head injury and stroke, we could not detect a relationship between Apo E4 phenotype and clinical outcome.

L3 ANSWER 15 OF 37 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 12

AN 2001:244042 CAPLUS

DN 135:190243

TI Clinical deterioration following improvement in the NINDS rt-PA stroke trial

AU Grotta, James C.; Welch, K. M. A.; Fagan, Susan C.; Lu, Mei; Frankel, Michael R.; Brott, Thomas; Levine, Steven R.; Lyden, Patrick D.

CS NINDS rt-PA Stroke Study Group, Department of Neurology, University of Texas Medical School, Houston, TX, 77030, USA

SO Stroke (2001), 32(3), 661-668  
CODEN: SJCCA7; ISSN: 0039-2499

PB Lippincott Williams & Wilkins

DT Journal

LA English

AB Little is known in regard to cerebral arterial reocclusion after successful thrombolysis. In the absence of arteriogram information, the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Trial investigators prospectively identified clinical deterioration following improvement (DFI) as a possible surrogate marker of cerebral arterial reocclusion after rt-PA-induced recanalization. Also, we identified any significant clinical deterioration (CD) even if not preceded by improvement. This observational analysis was designed to determine the incidence of DFI and CD in each treatment group, to identify baseline or posttreatment variables predictive of DFI or CD, and to determine any relationship between DFI, CD, and clinical outcome. DFI was defined as any 2-point deterioration on the NIH Stroke Scale after an initial 2-point improvement after treatment. CD was defined as any 4-point worsening after treatment compared with baseline. All data were collected prospectively by investigators blinded to treatment allocation. A noncontrast brain CT was mandated when a 2-point deterioration occurred. All cases were validated by a central review committee. DFI was identified in 81 of the 624 patients (13%); 44 were treated with rt-PA and 37 were treated with placebo ( $P=0.48$ ). DFI occurred more often in patients with a higher baseline NIH Stroke Scale score. CD within the first 24 h occurred in 98 patients (16% of all

patients); 43 were given rt-PA and 55 were given placebo (P=0.19). Baseline variables associated with CD included a less frequent use of prestroke aspirin and a higher incidence of early CT changes of edema or mass effect or dense middle cerebral artery sign. Patients with CD had higher rates of increased serum glucose and fibrin degradation products; and they also had higher rates of symptomatic intracranial hemorrhage and death. Patients who experienced either DFI or CD were less likely to have a 3-mo favorable outcome. We found no association between DFI, CD, and rt-PA treatment, and no clin. evidence to suggest reocclusion. Deterioration was strongly associated with stroke severity and poor outcome and was less frequent in patients whose stroke occurred while they were on aspirin.

RE.CNT 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

- L3 ANSWER 16 OF 37 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on  
STN  
AN 2001:159428 BIOSIS  
DN PREV200100159428  
TI Protective effects of pamiteplase, a modified t-PA, in a rat model of  
embolic stroke.  
AU Sumii, Toshihisa; Singhal, Aneesh B.; Asahi, Minoru; Shimizu-Sasamata,  
Masao; Suzuki, Masanori; Miyata, Keiji; Lo, Eng. H. [Reprint author]  
CS Neuroprotection Research Laboratory, Departments of Neurology and  
Radiology, Massachusetts General Hospital, MGH East 149-2322, Charlestown,  
MA, 02129, USA  
SO Neuroreport, (5 March, 2001) Vol. 12, No. 3, pp. 615-618. print.  
CODEN: NERPEZ. ISSN: 0959-4965.  
DT Article  
LA English  
ED Entered STN: 28 Mar 2001  
Last Updated on STN: 15 Feb 2002  
AB The effects of alteplase (tissue plasminogen activator, t-PA) and  
pamiteplase (a modified t-PA with longer half-life and increased potency)  
were compared in a clinically relevant model of embolic stroke. Rats were  
treated with pamiteplase (0.5 mg/kg or 1 mg/kg bolus), alteplase (10 mg/kg  
infusion) or normal saline. Pamiteplase (1 mg/kg) was as effective as  
alteplase in reducing 24 h brain infarct volumes, neurological deficit  
scores and residual clot grades. Cerebral blood flow recovery at 30 min  
after thrombolytic treatment was partial and did not correlate with 24 h  
infarct volumes or neurological deficits. However, there was good  
correlation between 24 h residual clot grades and infarct volumes,  
suggesting a delayed timeframe for pamiteplase- and alteplase-induced  
reperfusion.
- L3 ANSWER 17 OF 37 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 13  
AN 2001:169322 CAPLUS  
DN 134:336173  
TI Tissue plasminogen activator protects hippocampal neurons from  
oxygen-glucose deprivation injury  
AU Flavin, Michael P.; Zhao, Gang  
CS Department of Pediatrics, Queen's University, Kingston, ON, Can.  
SO Journal of Neuroscience Research (2001), 63(5), 388-394  
CODEN: JNREDK; ISSN: 0360-4012  
PB Wiley-Liss, Inc.  
DT Journal  
LA English  
AB We have previously shown that tissue plasminogen activator (tPA)  
participates in the neurotoxicity of microglial conditioned medium (MgCM).  
Killing of hippocampal neurons by MgCM was prevented by both plasminogen  
activator inhibitor-1 (PAI-1) and anti-tPA antibody. An  
N-methyl-D-aspartate (NMDA) receptor blocker protected neurons from MgCM,  
suggesting that this subtype of glutamate receptor is involved. Whereas  
glutamate receptor-mediated events are important in cerebral ischemia and

tPA has previously been shown to enhance excitotoxicity in hippocampus, we hypothesized that tPA would exaggerate oxygen glucose deprivation (OGD) injury in cultures of hippocampal neurons. Dissociated rat hippocampal cells were grown under conditions designed to optimize neuronal growth while minimizing glial replication. At 7-10 days, cultures were subjected to OGD for 2.5 h. Recombinant human tPA (1,000 IU) was added immediately after OGD. Viability was assessed 24 h later. Viable, apoptotic, and necrotic cells were classified and quantified based on staining patterns of acridine orange and ethidium bromide under fluorescence microscopy. TPA alone did not alter neuronal integrity. OGD produced significant neuronal death (viability reduced by 45%,  $P < 0.001$ ). TPA completely protected OGD-exposed cultures. Potential mechanisms of tPA protection were explored. Whereas tPA antibody abolished the protective effect of tPA, its proteolytic inhibitor PAI-1 did not alter the effect. The effect of tPA was tested in sep. free radical and excitatory amino acid insults. It did not protect neurons from hydrogen peroxide (1  $\mu\text{M}$ ), S-nitro-acetylpenicillamine (10  $\mu\text{M}$ ), glutamate (50  $\mu\text{M}$ ), or NMDA (10  $\mu\text{M}$ ) damage but significantly attenuated injury caused by 250  $\mu\text{M}$  kainate. We conclude that tPA is capable of protecting hippocampal neurons from OGD by a nonproteolytic action. The mechanism of protection was not defined, although attenuation of AMPA/kainate glutamate receptors may play a role.

RE.CNT 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 18 OF 37 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on  
STN  
AN 2001:432144 BIOSIS  
DN PREV200100432144  
TI Methodology for the Canadian Activase for Stroke Effectiveness Study  
(CASES).  
AU Hill, Michael D. [Reprint author]; Buchan, Alastair M.  
CS Department of Clinical Neurosciences, Foothills Medical Centre, University  
of Calgary, 1403 29th Street NW, MRG005 - Seaman Family MR Centre,  
Calgary, AB, T2N 2T9, Canada  
SO Canadian Journal of Neurological Sciences, (August, 2001) Vol. 28, No. 3,  
pp. 232-238. print.  
CODEN: CJNSA2. ISSN: 0317-1671.  
DT Article  
LA English  
ED Entered STN: 12 Sep 2001  
Last Updated on STN: 22 Feb 2002  
AB Background: Intravenous recombinant tissue plasminogen activator (tPA,  
alteplase) was conditionally licensed for the treatment of acute ischemic  
stroke (AIS) in Canada on February 17, 1999. As a condition of licensure,  
the Canadian Activase for Stroke Effectiveness Study (CASES) was  
established to monitor the use of alteplase for AIS in Canada. The study  
involves multiple stakeholders. Methods: CASES is a prospective registry  
of patients treated with alteplase for AIS. The purposes of this registry  
are to ensure the safety of the drug in the Canadian context, to assess  
effectiveness of alteplase for AIS and to gather further information to  
try to establish which patients are most likely to benefit from treatment.  
Results: Both community (n=25) and tertiary centres (n=35) have enrolled a  
total of 944 patients to date. Early results suggest that thrombolytic  
stroke treatment is both safe and effective among these centres.  
Conclusions: This paper outlines the development of and methods for the  
CASES study. The study is an example of a multi-stakeholder collaboration  
to advance the care of patients with acute stroke.

L3 ANSWER 19 OF 37 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 14  
AN 2001:116206 CAPLUS  
DN 135:147244  
TI Pharmacological effects of the spin trap agents N-t-butyl-phenylnitrone



(PBN) and 2,2,6,6-tetramethylpiperidine-N-oxyl (TEMPO) in a rabbit thromboembolic stroke model: Combination studies with the thrombolytic tissue plasminogen activator

AU Lapchak, Paul A.; Chapman, Deborah F.; Zivin, Justin A.  
CS Department of Neuroscience, University of California at San Diego, La Jolla, CA, 92093-0624, USA  
SO Stroke (2001), 32(1), 147-153  
CODEN: SJCCA7; ISSN: 0039-2499  
PB Lippincott Williams & Wilkins  
DT Journal  
LA English  
AB It has been proposed that spin trap agents such as N-t-butyl-phenylnitrone (PBN) may be useful as neuroprotective agents in the treatment of ischemia and stroke. However, to date, there is little information concerning the effectiveness of spin trap agents when administered in combination with the only Food and Drug Administration-approved pharmacol. agent for the treatment of stroke, the thrombolytic tissue plasminogen activator (tPA). Thus, we determined the effects of PBN when administered before tPA on hemorrhage and infarct rate and volume. We also compared the effects of PBN with those of 2,2,6,6-tetramethylpiperidine-N-oxyl (TEMPO), another spin trap agent that has a different chemical structure and trapping profile, on the incidence of infarcts and hemorrhage. One hundred sixty-five male New Zealand White rabbits were embolized by injecting a blood clot into the middle cerebral artery via a catheter. Five minutes after embolization, PBN or TEMPO (100 mg/kg) was infused i.v. Control rabbits received saline, the vehicle required to solubilize the spin traps. In tPA studies, rabbits were given i.v. tPA starting 60 min after embolization. Postmortem anal. included assessment of hemorrhage, infarct size and location, and clot lysis. In the control group, the hemorrhage rate after a thromboembolic stroke was 24%. The amount of hemorrhage was significantly increased to 77% if the thrombolytic tPA was administered. The rabbits treated with PBN in the absence of tPA had a 91% incidence of hemorrhage compared with 33% for the TEMPO-treated group. In the combination drug-treated groups, the PBN/tPA group had a 44% incidence of hemorrhage, and the TEMPO/tPA group had a 42% incidence of hemorrhage. TPA, PBN/tPA, and TEMPO/tPA were similarly effective at lysing clots (49%, 44%, and 33%, resp.) compared with the 5% rate of lysis in the control group. There was no significant effect of drug combinations on the rate or volume of infarcts. This study suggests that certain spin trap agents may have deleterious effects when administered after an embolic stroke. However, spin trap agents such as PBN or TEMPO, when administered in combination with tPA, may improve the safety of tPA by reducing the incidence of tPA-induced hemorrhage. Overall, the therapeutic benefit of spin trap agents for the treatment of ischemic stroke requires addnl. scrutiny before they can be considered "safe" therapeutics.

RE.CNT 63 THERE ARE 63 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 20 OF 37 CAPLUS COPYRIGHT 2004 ACS on STN  
AN 2001:245648 CAPLUS  
DN 135:189522  
TI Thrombolysis in ischaemic stroke - present and future: Role of combined therapy  
AU Kaste, Markku  
CS Department of Neurology, University of Helsinki, Helsinki, FIN-00029, Finland  
SO Cerebrovascular Diseases (Basel, Switzerland) (2001), 11(Suppl. 1), 55-59  
CODEN: CDISE7; ISSN: 1015-9770  
PB S. Karger AG  
DT Journal; General Review  
LA English  
AB A review with 33 refs. ECASS I, the NINDS trial and ECASS II showed that thrombolysis with rt-PA is effective in acute ischemic stroke. In ECASS

I, there was a safety problem because of increased mortality, while the results of the NINDS trial led the FDA to approve the use of rt-PA in ischemic stroke. The safety was no more a problem in ECASS II. A meta-anal. of those three trials revealed that thrombolysis decreases the risk of death and dependency. For each 1,000 patients treated within 3 h, there will be 140 less dead or dependent, and 90 less if the treatment is given within 6 h. These data support the view that rt-PA should be part of the management of acute ischemic stroke within 3 h, and probably beyond, in selected patients and experienced centers. Thrombolysis within a 3-h time frame is also likely to result in net cost savings. All trials studying neuroprotecting agents have failed in man, although they have been successful in exptl. animals. A combination of thrombolysis and a neuroprotecting agent or a combination of two neuroprotecting agents have been effective in exptl. stroke, but the only clin. study with combination therapy (rt-PA with or without lubeluzole) was terminated prematurely before the planned population was enrolled. This was not because of safety problems but because the sponsor lost interest. In future, there will most likely be others to challenge the strategy of the combined therapy, and this strategy will sooner or later lead to a benchmark breakthrough. It is unlikely that any of these therapies or their combinations will work without well-organized services, which can provide fast and efficient medical care. Without such a triage, any drug will be unlikely to have a major impact on stroke recovery.

RE.CNT 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 21 OF 37 MEDLINE on STN  
AN 2002167245 MEDLINE  
DN PubMed ID: 11898496  
TI New insights on thrombolytic treatment of acute ischemic stroke.  
AU Meschia J F; Brott T G  
CS Department of Neurology, Mayo Clinic, 4500 San Pablo Road, Jacksonville, FL 32224, USA.. meschia.james@mayo.edu  
SO Current neurology and neuroscience reports, (2001 Jan) 1 (1) 19-25. Ref: 36  
Journal code: 100931790. ISSN: 1528-4042.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
General Review; (REVIEW)  
(REVIEW, TUTORIAL)  
LA English  
FS Priority Journals  
EM 200204  
ED Entered STN: 20020320  
Last Updated on STN: 20020409  
Entered Medline: 20020408  
AB In 1995, a two-part randomized trial showed the efficacy of intravenous tissue plasminogen activator (tPA) when given within 3 hours of onset of symptoms of acute ischemic stroke. Two subsequent trials were unable to extend the therapeutic window of intravenous tPA beyond 3 hours. A phase IV study performed by experienced stroke centers showed an acceptably low symptomatic intracerebral hemorrhage rate for intravenous tPA of only 3%, whereas a review of the Cleveland area experience showed a disturbingly high rate of symptomatic intracerebral hemorrhage of 15.7%. The Prolyse in Acute Cerebral Thromboembolism (PROACT) II study showed efficacy of intra-arterial pro-urokinase and intravenous heparin over intravenous heparin alone when given within 6 hours of onset of symptoms to patients with thrombotic occlusion of the proximal middle cerebral artery. Additional controlled investigations of intra-arterial thrombolytic therapy are needed. **Neuroprotectants** in combination with intravenous tPA have yet to show improved efficacy over the use of tPA alone.

L3 ANSWER 22 OF 37 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on  
 STN  
 AN 2001:45389 BIOSIS  
 DN PREV200100045389  
 TI Intravenous tissue plasminogen activator for acute ischemic stroke: A  
 Canadian hospital's experience.  
 AU Chapman, Kristine M.; Woolfenden, Andrew R. [Reprint author]; Graeb,  
 Douglas; Johnston, Dean C. C.; Beckman, Jeff; Schulzer, Michael; Teal,  
 Phil A.  
 CS V.G.H. Stroke Study Office, 214-855 West 12th Ave, Vancouver, BC, V5Z 3J5,  
 Canada  
 vghsso@interchange.ubc.ca  
 SO Stroke, (December, 2000) Vol. 31, No. 12, pp. 2920-2924. print.  
 CODEN: SJCCA7. ISSN: 0039-2499.  
 DT Article  
 LA English  
 ED Entered STN: 17 Jan 2001  
 Last Updated on STN: 12 Feb 2002  
 AB Background and Purpose: In the United States, tissue plasminogen activator  
 (tPA) was approved for treatment of acute ischemic stroke in 1996. Its  
 use has only recently been approved in Canada. We sought to evaluate the  
 safety, feasibility, and efficacy of treatment in a Canadian hospital  
 setting. Methods: A combined retrospective and prospective review is  
 presented of 46 consecutive patients treated with intravenous tPA at our  
 hospital with a treatment protocol similar to that of the National  
 Institute of Neurological Disorders and Stroke (NINDS) trial. Results:  
 Symptomatic intracranial hemorrhage at 36 hours occurred in 1 patient  
 (2.2%). The median time to treat was 165 minutes, with a median  
 "door-to-needle" time of 84 minutes. Compared with patients presenting  
 initially at our hospital, patients transferred from another institution  
 for tPA therapy were treated closer to the 3-hour time window (mean 173  
 versus 148 minutes,  $P < 0.001$ ) but had a shorter door-to-needle time (43  
 versus 102 minutes,  $P < 0.001$ ). For every 10 minutes closer to the 3-hour  
 time window that any patient arrived at the hospital, 7 minutes was saved  
 in the door-to-needle time (correlation coefficient 0.9,  $P < 0.001$ ).  
 Patient outcome did not differ from that in the NINDS trial ( $P > 0.75$ ).  
 Conclusions: Our safety and patient outcome data compare favorably with  
 NINDS and Phase IV data. Although a 3-hour treatment window was feasible,  
 the median door-to-needle time lengthened as more treatment time was  
 available and the door-to-needle time was beyond recommended standards.  
 This review has prompted changes in our community to improve treatment  
 efficiency.

L3 ANSWER 23 OF 37 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 15  
 AN 2000:842903 CAPLUS  
 DN 135:40804  
 TI Combined intravenous and intra-arterial recombinant tissue plasminogen  
 activator in acute ischemic stroke  
 AU Ernst, Robert; Pancioli, Arthur; Tomsick, Thomas; Kissela, Brett; Woo,  
 Daniel; Kanter, Daniel; Jauch, Edward; Carrozzella, Janice; Spilker,  
 Judith; Broderick, Joseph  
 CS Department of Radiology, Section of Neuroradiology, University of  
 Cincinnati Medical Center, Cincinnati, OH, 45267-0762, USA  
 SO Stroke (2000), 31(11), 2552-2557  
 CODEN: SJCCA7; ISSN: 0039-2499  
 PB Lippincott Williams & Wilkins  
 DT Journal  
 LA English  
 AB A retrospective anal. was performed on 20 consecutive patients who  
 presented with severe acute ischemic stroke and were evaluated for a  
 combined i.v. and local intra-arterial (IA) recombinant tissue plasminogen  
 activator (rtPA) thrombolytic approach within 3 h of onset. Twenty  
 consecutive patients with carotid artery distribution strokes were

evaluated and treated using a combined i.v. and IA rtPA approach over a 14-mo period (Sept. 1998 to Oct. 1999). RtPA (0.6 mg/kg) was given i.v. (maximum dose 60 mg); 15% of the IV dose was given as bolus, followed by a continuous infusion over 30 min. A maximal IA dose, up to 0.3 mg/kg or 24 mg, whichever was less, was given over a maximum of 2 h. IV treatment was initiated within 3 h in 19 of 20 patients. All 20 patients underwent angiog., and 16 of 20 patients received local IA rtPA. The median baseline National Institutes of Health Stroke Scale (NIHSS) score for the 20 patients was 21 (range 11 to 31). The median time from stroke onset to IV treatment was 2 h and 2 min, and median time to initiation of IA treatment was 3 h and 30 min. Ten patients (50%) recovered to a modified Rankin Scale (mRS) of 0 or 1; 3 patients (15%), to an mRS of 2; and 5 patients (25%), to an mRS of 4 or 5. One patient (5%) developed a symptomatic intracerebral hemorrhage and eventually died. One other patient (5%) expired because of complications from the stroke. We believe that the greater-than-expected proportion of favorable outcomes in these patients with severe ischemic stroke reflects the short time to initiation of both IV and IA thrombolysis.

RE.CNT 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 24 OF 37 CAPLUS COPYRIGHT 2004 ACS on STN  
AN 2001:119249 CAPLUS  
DN 135:146513  
TI Current and future therapies for ischemic cerebrovascular disease  
AU Yanaka, Kiyoyuki; Kujiraoka, Yuji; Okazaki, Masao; Asakawa, Hiroyuki;  
Kato, Noriyuki; Matsumaru, Yuji; Nose, Tadao  
CS Department of Neurosurgery, Institute of Clinical Medicine, University of  
Tsukuba, Ibaraki, 305-8575, Japan  
SO Drugs of Today (2000), 36(12), 807-815  
CODEN: MDACAP; ISSN: 0025-7656  
PB Prous Science  
DT Journal; General Review  
LA English  
AB A review with 63 refs. Stroke is the third leading cause of death in the adult population. It makes great demands on patients, who must not only survive the complications of the acute stages but also must cope with the great phys. and economic costs of long-term disabilities. Therefore, there is an urgent need to establish generally useful treatments for ischemic stroke. Currently, there are three treatment approaches based on pathophysiol. concepts derived from basic research: (i) pharmacol. strategies for arterial recanalization, (ii) neuronal protection and (iii) the inhibition of undesirable damaging host responses. The key to current treatment is the emergent administration of tissue plasminogen activator (t-PA). Thrombolytic treatment improves outcome when given to carefully selected patients within 3 h of stroke onset. Numerous neuroprotective agents have been developed in the last decade, and a new wave of therapies is now on the horizon that could potentially minimize ischemic brain damage. This article highlights recent advances in pharmacol. interventions for ischemic stroke.

RE.CNT 63 THERE ARE 63 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 25 OF 37 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN  
AN 2000:456290 BIOSIS  
DN PREV200000456290  
TI Treatment of acute ischemic stroke.  
AU Brott, Thomas [Reprint author]; Bogousslavsky, Julien  
CS Department of Neurology, Mayo Clinic, 4500 San Pablo Rd., Jacksonville, FL, 32224, USA  
SO New England Journal of Medicine, (September 7, 2000) Vol. 343, No. 10, pp. 710-722. print.

CODEN: NEJMAG. ISSN: 0028-4793.

DT Article  
 General Review; (Literature Review)

LA English  
 ED Entered STN: 25 Oct 2000  
 Last Updated on STN: 10 Jan 2002

L3 ANSWER 26 OF 37 CAPLUS COPYRIGHT 2004 ACS on STN  
 AN 2001:339876 CAPLUS  
 DN 135:221012  
 TI Changes in coagulation and tissue plasminogen activator after the  
 treatment of cerebral infarction with lumbrokinase  
 AU Jin, Lirong; Jin, Huiming; Zhang, Guoping; Xu, Guizhi  
 CS Department of Neurology, Zhongshan Hospital, Shanghai Medical University,  
 Shanghai, Peop. Rep. China  
 SO Clinical Hemorheology and Microcirculation (2000), 23(2-4), 213-218  
 CODEN: CHMIFQ; ISSN: 1386-0291  
 PB IOS Press  
 DT Journal  
 LA English  
 AB This paper aimed to investigate the effect of lumbrokinase on the  
 anticoagulation and fibrinolysis in treating cerebral infarction.  
 Lumbrokinase was used in patients with cerebral infarction. Patients were  
 randomly divided into treatment group (n = 31) and control group (n = 20).  
 Single blind method was used in this investigation. The Chinese stroke  
 score was used to evaluate the results of treatment before and after  
 administration of lumbrokinase. Kaolin partial thromboplastin time  
 (KPTT), prothrombin time (PT), fibrinogen content, vWF content were  
 analyzed, and tissue plasminogen activator (t-PA) activity, plasminogen  
 activator inhibitor (PAI) activity, D-dimer level were assayed. In both  
 groups, the stroke score decreased after administration, but in the  
 treatment group, it was more obvious. In the treatment group, KPTT was  
 prolonged, t-PA activity and D-dimer level increased, while the content of  
 fibrinogen decreased significantly. There were no significant changes of  
 PT and PAI activity in both groups. It is concluded that lumbrokinase is  
 beneficial to the treatment of cerebral infarction. The effect of  
 lumbrokinase is related to the inhibition of intrinsic coagulation pathway  
 and the activation of fibrinolysis via an increase of t-PA activity.

RE.CNT 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 27 OF 37 ADISCTI COPYRIGHT (C) 2004 Adis Data Information BV on  
 STN  
 AN 2000:10351 ADISCTI  
 DN 800826243  
 TI Safety and efficacy of combined clomethiazole and tPA for acute  
 stroke-CLASS-T: a pilot study.  
 ADIS TITLE: Alteplase +- clomethiazole: therapeutic use.  
 Stroke  
 CLASS-T: a pilot study.  
 AU Lyden P D; CLASS IHT Investigators.  
 CS San Diego, California, USA.  
 SO Neurology (Apr 11, 2000), Vol. 54 (Suppl. 3), pp. 88  
 DT Study  
 RE Neurological Disorders| Antithrombotics  
 FS Summary  
 LA English  
 WC 407

L3 ANSWER 28 OF 37 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on  
 STN  
 AN 2000:223123 BIOSIS  
 DN PREV200000223123

TI Neuroprotective effect of PB007 on focal and multifocal ischemic injury of central nervous tissue in the rabbit.  
AU Araneo, Barbara A. [Reprint author]; Zivin, Justin A.  
CS Salt Lake City, UT, USA  
SO Neurology, (April 11, 2000) Vol. 54, No. 7 Supp. 3, pp. A67. print.  
Meeting Info.: 52nd Annual Meeting of the American Academy of Neurology. San Diego, CA, USA. April 29-May 06, 2000. American Academy of Neurology. CODEN: NEURAI. ISSN: 0028-3878.  
DT Conference; (Meeting)  
Conference; Abstract; (Meeting Abstract)  
Conference; (Meeting Poster)  
LA English  
ED Entered STN: 31 May 2000  
Last Updated on STN: 5 Jan 2002

L3 ANSWER 29 OF 37 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

AN 2001:78060 BIOSIS

DN PREV200100078060

TI Differential effects of the spin trap agent PBN on hemorrhage rate following a thromboembolic stroke: a combination study with the thrombolytic tPA.

AU Zivin, J. A. [Reprint author]; Chapman, D. F.; Lapchak, P. A.

CS Univ California San Diego Sch Med, La Jolla, CA, USA

SO Society for Neuroscience Abstracts, (2000) Vol. 26, No. 1-2, pp. Abstract No.-287.4. print.

Meeting Info.: 30th Annual Meeting of the Society of Neuroscience. New Orleans, LA, USA. November 04-09, 2000. Society for Neuroscience. ISSN: 0190-5295.

DT Conference; (Meeting)

Conference; Abstract; (Meeting Abstract)

LA English

ED Entered STN: 7 Feb 2001

Last Updated on STN: 12 Feb 2002

AB Tissue plasminogen activator (tPA) is now gaining increasing acceptance for acute stroke management, even though there is a small window of opportunity for treatment and a potentially dangerous side effect, hemorrhages. We have focused on developing compounds that can be administered with tPA in order to increase its safety. We occluded the MCA of rabbits with radiolabelled blood clots. Five minutes after embolization we administered PBN (100 mg/kg IV) or vehicle in combination with tPA (60 minutes after embolization(3.3mgkg-1 tPA)). Hemorrhage after embolic stroke was detected in 24% of the control group. TPA induced hemorrhage in 77% of the tPA-treated group. The rabbits treated with PBN had a 91% incidence of hemorrhage. However, when the combination of PBN and tPA was administered to rabbits, there was only a 44% incidence of hemorrhage. Both tPA and tPA/PBN were similarly effective at lysing clots. In the absence of tPA, the spin trap agent PBN significantly increased hemorrhage rate (by 279%) following an embolic stroke. This suggests that PBN when administered prior to reperfusion may be deleterious to vessel membranes. However, following reperfusion, PBN significantly reduced the tPA-induced hemorrhage rate (by 43%) following an embolic stroke. This observation suggests that, at least in part, hydroxyl radicals mediate tPA-induced hemorrhage following an embolic stroke when tPA induces cerebral reperfusion. Overall, combination therapy with PBN and tPA significantly attenuates the major side effect of tPA (PBN was purchased from SIGMA and tPA was supplied by Genentech Inc.).

L3 ANSWER 30 OF 37 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

AN 2001:76018 BIOSIS

DN PREV200100076018

TI Fibrin deposition exacerbates axonal damage.

AU Akassoglou, K. [Reprint author]; Kombrinck, K.; Salles, F.; Kollias, G.;  
Probert, L.; Degen, J.; Strickland, S.  
CS State University of New York, Stony Brook, NY, USA  
SO Society for Neuroscience Abstracts, (2000) Vol. 26, No. 1-2, pp. Abstract  
No.-121.17. print.  
Meeting Info.: 30th Annual Meeting of the Society of Neuroscience. New  
Orleans, LA, USA. November 04-09, 2000. Society for Neuroscience.  
ISSN: 0190-5295.  
DT Conference; (Meeting)  
Conference; Abstract; (Meeting Abstract)  
LA English  
ED Entered STN: 7 Feb 2001  
Last Updated on STN: 12 Feb 2002  
AB To identify the role of tPA/plasmin extracellular proteolysis in neuronal  
damage we performed sciatic nerve injury in mice lacking tPA or  
plasminogen. Axonal degeneration was exacerbated in the absence of tPA or  
plasminogen. Axonal damage correlated with extensive fibrin deposition,  
and the increased axonal degeneration phenotype in tPA- or  
plasminogen-deficient mice was abolished by depleting fibrinogen. This  
result shows that tPA/plasmin protects axons from degeneration due to its  
proteolytic effect on fibrin(ogen). In the CNS, in a TNF transgenic  
animal model of multiple sclerosis, fibrin deposition colocalized with  
active demyelinating plaques in the spinal cord. There was no  
upregulation of proteolytic activity or tPA protein, suggesting that  
limited fibrinolytic activity in the CNS could contribute to chronic  
damage in neurodegenerative disorders. The molecular mechanism to explain  
the pathogenic effect of fibrin on axonal demyelination is under  
investigation.

L3 ANSWER 31 OF 37 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on  
STN  
AN 2001:78059 BIOSIS  
DN PREV200100078059  
TI Metalloproteinase inhibition using BB-94 reduces thrombolytic  
(tPA)-induced hemorrhage following a thromboembolic stroke.  
AU Lapchak, P. A. [Reprint author]; Chapman, D. F.; Zivin, J. A.  
CS UCSD, La Jolla, CA, USA  
SO Society for Neuroscience Abstracts, (2000) Vol. 26, No. 1-2, pp. Abstract  
No.-287.3. print.  
Meeting Info.: 30th Annual Meeting of the Society of Neuroscience. New  
Orleans, LA, USA. November 04-09, 2000. Society for Neuroscience.  
ISSN: 0190-5295.  
DT Conference; (Meeting)  
Conference; Abstract; (Meeting Abstract)  
LA English  
ED Entered STN: 7 Feb 2001  
Last Updated on STN: 12 Feb 2002  
AB Thrombolysis is quite beneficial for stroke treatment even though there is  
a potentially dangerous side effect, hemorrhages. We have focused on  
developing compounds that could be administered with tPA to reduce  
hemorrhage rate. Recent studies suggest that various metalloproteinases  
(MMP's) are important in TNF-alpha production and membrane and vessel  
remodeling following ischemia. We determined if MMP inhibition affected  
hemorrhage rate following a stroke. We occluded the MCA of rabbits with  
radiolabelled blood clots. Five minutes after embolization, we  
administered the nonspecific MMP inhibitor BB-94 (30 mg/kg, SC).  
Additional rabbits received BB-94 in combination with tPA (60 min post  
embolization (3.3mg/kg tPA)). Hemorrhage after embolic stroke was  
detected in 24% of the control group. TPA induced hemorrhage in 77% of  
the tPA-treated group. The rabbits treated with BB-94 had an 18%  
incidence of hemorrhage ( $p > 0.05$  compared to control). However, in BB-94  
and tPA treated rabbits, there was only a 41% incidence of hemorrhage  
(compared to 77% in the tPA group,  $p < 0.05$ ). Both tPA and tPA/BB-94 were

similarly effective at lysing clots, 49% and 35% ( $p < 0.05$ ), respectively, when compared to the 5% rate of lysis in the control group. The MMP inhibitor BB-94 significantly reduced (by 47%) the tPA-induced hemorrhage rate following embolic stroke. Our data suggest that MMP inhibition attenuates mechanisms involved in tPA-induced hemorrhage. This novel form of combination therapy may show promise as a treatment strategy for acute stroke. (BB-94 was supplied by British Biotech, Oxford, UK and tPA was supplied by Genentech Inc South San Francisco, CA).

L3 ANSWER 32 OF 37 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on  
STN DUPLICATE 16  
AN 1999:305799 BIOSIS  
DN PREV199900305799  
TI Recombinant tissue plasminogen activator reduces infarct size after  
reversible thread occlusion of middle cerebral artery in mice.  
AU Kilic, E.; Hermann, D. M.; Hossmann, K.-A. [Reprint author]  
CS Max-Planck-Institut fuer Neurologische Forschung, Gleueler Str. 50,  
D-50931, Cologne, Germany  
SO Neuroreport, (Jan. 18, 1999) Vol. 10, No. 1, pp. 107-111. print.  
CODEN: NERPEZ. ISSN: 0959-4965.  
DT Article  
LA English  
ED Entered STN: 12 Aug 1999  
Last Updated on STN: 12 Aug 1999  
AB IT has been suggested that tissue plasminogen activator (tPA), which is  
widely used for the thrombolytic treatment of stroke, exhibits neurotoxic  
side effects. To test this hypothesis, mice exposed to 90 min  
non-thrombotic middle cerebral artery thread occlusion were treated with  
10 mg/kg recombinant tPA (rt-PA) at 15 min after the onset of vascular  
occlusion. Measurements of blood flow, infarct volume, brain swelling and  
neurological performance revealed faster recirculation and a significant  
reduction of ischemic injury in rt-PA-treated animals. These data are at  
variance with previous reports on tPA neurotoxicity and demonstrate, on  
the contrary, that tPA protects the brain even after non-thrombotic  
vascular occlusion.

L3 ANSWER 33 OF 37 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on  
STN  
AN 1998:125971 BIOSIS  
DN PREV199800125971  
TI Tissue plasminogen activator (tPA) increases neuronal damage after focal  
cerebral ischemia in wild-type and tPA-deficient mice.  
AU Wang, Yanming F.; Tsirka, Stella E.; Strickland, Sidney; Stieg, Philip E.;  
Soriano, Sulpicio G.; Lipton, Stuart A. [Reprint author]  
CS Cerebrovascular NeuroSci. Res. Inst., Brigham and Women's Hosp./Harvard  
Med. Sch., 221 Longwood Ave., LMRC First Floor, Boston, MA 02115, USA  
SO Nature Medicine, (Feb., 1998) Vol. 4, No. 2, pp. 228-231. print.  
ISSN: 1078-8956.  
DT Article  
LA English  
ED Entered STN: 5 Mar 1998  
Last Updated on STN: 5 Mar 1998  
AB Intravenous tissue plasminogen activator (tPA) is used to treat acute  
stroke because of its thrombolytic activity and its ability to restore  
circulation to the brain. However, this protease also promotes  
neurodegeneration after intracerebral injection of excitotoxins such as  
glutamate, and neuronal damage after a cerebral infarct is thought to be  
mediated by excitotoxins. To investigate the effects of tPA on cerebral  
viability during ischemia/reperfusion, we occluded the middle cerebral  
artery in wild-type and tPA-deficient mice with an intravascular filament.  
This procedure allowed us to examine the role of tPA in ischemia,  
independent of its effect as a thrombolytic agent. tPA-deficient mice  
exhibited approx 50% smaller cerebral infarcts than wild-type mice.



Intravenous injection of tPA into tPA-/- or wild-type mice produced larger infarcts, indicating that tPA can increase stroke-induced injury. Since tPA promotes desirable (thrombolytic) as well as undesirable (neurotoxic) outcomes during stroke, future therapies should be aimed at countering the excitotoxic damage of tPA to afford even better neuroprotection after an acute cerebral infarct.

L3 ANSWER 34 OF 37 CAPLUS COPYRIGHT 2004 ACS on STN

AN 1997:381013 CAPLUS

DN 126:338854

TI Infusions of neuroprotectants and thrombolytic agents

IN Hantson, Ludwig Norbert Michel; De Ryck, Marc Roger; Tritsmans, Luc Remi Mathilde

PA Janssen Pharmaceutica N.V., Belg.; Hantson, Ludwig Norbert Michel; De Ryck, Marc Roger; Tritsmans, Luc Remi Mathilde

SO PCT Int. Appl., 19 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9715323	A1	19970501	WO 1996-EP4609	19961021
	W: AL, AM, AU, BB, BG, BR, CA, CN, CZ, EE, GE, HU, IL, IS, JP, KG, KR, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9674913	A1	19970515	AU 1996-74913	19961021
	EP 862457	A1	19980909	EP 1996-937215	19961021
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, LT, LV, FI				
	JP 11515010	T2	19991221	JP 1996-516280	19961021
PRAI	EP 1995-202887	A	19951025		
	EP 1996-201642	A	19960612		
	WO 1996-EP4609	W	19961021		

OS MARPAT 126:338854

AB Infusions comprising a neuroprotectant and thrombolytic agent as a combined preparation for simultaneous, sep. or sequential use in the treatment of acute ischemic stroke are claimed. The neuroprotectant is used for the preparation of a medicament for preventing or delaying the process of infarction accompanying acute ischemic stroke from being completed, thus enlarging the inclusion period during which the above combined preparation can be administered safely. To a solution of 11.6 g lubeluzole in 700 mL dichloromethane at -10° was added 6.7 g m-chlorobenzoic acid and stirred for 24 h, then washed with an aqueous ammonia solution and water. The organic phase was dried, filtered, and evaporated to yield 9.6 g of (-)-[cis]lubeluzole N-oxide hemihydrate (I). The anti-hypoxic properties of I is demonstrated in rats.

L3 ANSWER 35 OF 37 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

AN 1998:69025 BIOSIS

DN PREV199800069025

TI Does effect of a neuroprotective agent on volume of experimental animal cerebral infarct predict effect of the agent on clinical outcome in human stroke?.

AU Jonas, S. [Reprint author]; Tran, A. Q.; Eisenberg, E.; Azam, M.; Viera, D.; Grumet, S.

CS Dep. Neurol., NYU Sch. Med., 462 First Ave., New York, NY 10016, USA

SO Slikker, W., Jr. [Editor]; Tremblay, B. [Editor]. Ann. N. Y. Acad. Sci., (1997) pp. 281-287. Annals of the New York Academy of Sciences;

Neuroprotective agents. print.

Publisher: New York Academy of Sciences, 2 East 63rd Street, New York, New York 10021, USA. Series: Annals of the New York Academy of Sciences.

Meeting Info.: Third International Conference on Neuroprotective Agents: Clinical and Experimental Aspects. Lake Como, Italy. September 9-12, 1996. New York Academy of Sciences.

CODEN: ANYAA9. ISSN: 0077-8923. ISBN: 1-57331-092-1 (cloth), 1-57331-093-X (paper).

DT Book

Conference; (Meeting)

Book; (Book Chapter)

Conference; (Meeting Paper)

LA English

ED Entered STN: 30 Jan 1998

Last Updated on STN: 30 Jan 1998

L3 ANSWER 36 OF 37 CAPLUS COPYRIGHT 2004 ACS on STN

AN 1997:559755 CAPLUS

DN 127:229412

TI The NINDS t-PA acute stroke study

AU Grotta, J.

CS Department of Neurology, University of Texas Houston Medical School, Houston, TX, USA

SO Pharmacology of Cerebral Ischemia 1996, [International Symposium on Pharmacology of Cerebral Ischemia], 6th, Marburg, July 21-24, 1996 (1996), 701-710. Editor(s): Kriegelstein, Josef. Publisher: Medpharm Scientific Publishers, Stuttgart, Germany.

CODEN: 64YHA7

DT Conference

LA English

AB The NINDS t-PA trial was published in Dec., 1995. The trial was really two sep. but sequential and comparable studies; the first (291 patients) to evaluate outcome at 24 h but including 3 mo outcome, and the second (333 patients) to evaluate 3 mo outcome. The protocols were otherwise exactly alike and investigators remained blinded to the outcome of Part 1 until both parts were completed. Significantly improved outcome in t-PA treated patients was found in both studies. There was a 30-50% relative (12% absolute) increase in favorable outcome (no disability or neurol. deficit on the clin. assessment scales) at 3 mo for those patients who received t-PA (0.9 mg./kg. IV over one hour with 10% given as a bolus over the first minute) within 3 h of stroke onset. Using the Barthel Index, 50% of treated patients scored  $\geq 95$  compared to 38% of placebo patients. Unlike all the other thrombolytic trials, there was no difference in mortality between those receiving t-PA and placebo; death including those patients with symptomatic hemorrhage was 17% with t-PA vs. 21% with placebo. Symptomatic hemorrhage occurred in the first 36 h in 6.4% receiving t-PA vs. 0.6% receiving placebo. There was a strong trend toward improvement in neurol. score within the first 24 h in patients treated with t-PA. While there was no difference in the number of patients showing a 4 point improvement on the NIH Stroke Scale (NIHSS), the median NIHSS was significantly better at 24 h in treated patients, and more t-PA patients showed complete recovery. The two parts can be combined together for exploratory analyses. These revealed that all sub-groups of treated patients appeared to benefit. For instance, patients with all stroke sub-types (based on clin. assessment) and either time strata to treatment (0-90 min or 91 to 180 min) showed a favorable response to t-PA. As with other trials, outcome in all patients was worse with advanced age, diabetes, worse baseline neurol. deficit, and baseline CT abnormalities indicating early infarction ( $\leq 5\%$  of the overall population in the NINDS study). The possibility that some combination of these variables might identify a non-responding group is the subject of ongoing evaluation as are formal cost-benefit and CT analyses.

L3 ANSWER 37 OF 37 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 17

AN 1996:69415 CAPLUS

DN 124:165092

TI Influence of a "Brain Protector" drug 21-amino steroid on the effects of experimental embolic stroke treated by thrombolysis

AU Orozco, Jose; Mendel, Richard C.; Hahn, Michael R.; Guthkelch, Ari N.; Carter, L. Philip

CS Health Sciences Center, University Arizona, Tucson, AZ, USA

SO Neurological Research (1995), 17(6), 423-5

CODEN: NRESZD; ISSN: 0161-6412

PB Forefront Publishing

DT Journal

LA English

AB This study was designed to evaluate the effects of tissue-type plasminogen activator (tPA) and 21-amino steroid (U74006F) in exptl. embolic stroke in rabbits. The size of infarction from embolism was compared to controls with tPA alone, 21-amino steroid alone, and in combination. The middle cerebral artery of the rabbit was embolized by injecting an arterial ("white") thrombus in the right internal carotid artery. The rabbit treatment was 2 mg kg<sup>-1</sup> of tissue-type plasminogen activator and/or 3 mg kg<sup>-1</sup> of 21 amino steroid started at 2 h post-embolization. The animals were terminated 4 h post-treatment and brains were examined for evidence of ischemia and/or hemorrhage. Administration of tissue-type plasminogen activator and/or 21-amino steroid in the raw data show that there is a tendency for all treatments to reduce the ischemic volume when compared to the control group, also it is evident the standard deviation of these ests. is rather large when compared to the differences between treatments. The results of the anal. of variance shows that the differences expressed are not statistically significant. (No statistical differences were found between the treatment groups and the control group.). The results show that administration of tissue-type plasminogen activator and/or 21 amino steroid at 2 h post-embolization alone or in simultaneous administration does not significantly reduce the volume of infarction. Further studies need to be addressed in regards to the region of viable brain in the peri-infarct area, and in reducing the time to treatment.